

JAN 12 2000

Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, NJ 08543-4000

Attention: Joseph A. Linkewich, Pharm.D.
Director, U.S. Regulatory Liaison
Worldwide Regulatory Affairs

Dear Dr. Linkewich:

Please refer to your supplemental new drug application dated December 2, 1999, received December 7, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for HYDREA ® (hydroxyurea capsules, USP).

This supplemental new drug application provides labeling revisions in accordance with our approval letter for NDA 16-295/SLR-026 dated August 11, 1999.

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted labeling (package insert submitted December 2, 1999) with the revisions listed below. Accordingly, the supplemental application is approved effective on the date of this letter. The following revisions should be included at your next printing.

1. In the **HOW SUPPLIED** section, **Storage** subsection, please revise the recommended storage conditions to the following:

Store at 25°C (77°); excursion permitted to 15°C-30°C (59°-86°F)
[see USP Control Room Temperature]
Keep tightly closed.

2. In the **PRECAUTIONS** section, **Information for Patients** subsection, please add the following sentence at the end of the paragraph: "The medication should be kept away from children and pets."

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

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We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Dotti Pease, Project Manager, at (301) 594-5742.

Sincerely,

Richard Pazdur, M.D.
Division Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research



Rx only

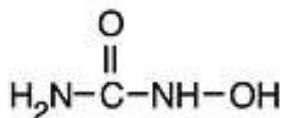
HYDREA[®]

(hydroxyurea capsules, USP)

DESCRIPTION

HYDREA[®] (hydroxyurea capsules, USP) is an antineoplastic agent, available for oral use as capsules providing 500 mg hydroxyurea. Inactive ingredients: citric acid, colorants (D&C Yellow No. 10, FD&C Blue No.1, FD&C Red 40 and D&C Red 28), gelatin, lactose, magnesium stearate, sodium phosphate, and titanium dioxide.

Hydroxyurea occurs as an essentially tasteless, white crystalline powder. Its structural formula is:



CLINICAL PHARMACOLOGY

Mechanism of Action

The precise mechanism by which hydroxyurea produces its antineoplastic effects cannot, at present, be described. However, the reports of various studies in tissue culture in rats and man lend support to the hypothesis that hydroxyurea causes an immediate inhibition of DNA synthesis without interfering with the synthesis of ribonucleic acid or of protein. This hypothesis explains why, under certain conditions, hydroxyurea may induce teratogenic effects.

Three mechanisms of action have been postulated for the increased effectiveness of concomitant use of hydroxyurea therapy with irradiation on squamous cell (epidermoid) carcinomas of the head and neck. *In vitro* studies utilizing Chinese hamster cells suggest that hydroxyurea (1) is lethal to normally radioresistant S-stage cells, and (2) holds other cells of the cell cycle in the G1 or pre-DNA synthesis stage where they are most susceptible to the effects of irradiation. The third mechanism of action has been theorized on the basis of *in vitro* studies of HeLa cells: it appears that hydroxyurea, by inhibition of DNA synthesis, hinders the normal repair process of cells damaged but not killed by irradiation, thereby decreasing their survival rate; RNA and protein syntheses have shown no alteration.

Pharmacokinetics

Absorption

Hydroxyurea is readily absorbed after oral administration. Peak plasma levels are reached in 1 to 4 hours after an oral dose. With increasing doses, disproportionately greater mean peak plasma concentrations and AUCs are observed.

There are no data on the effect of food on the absorption of hydroxyurea.

Distribution

Hydroxyurea distributes rapidly and widely in the body with an estimated volume of distribution approximating total body water.

Plasma to ascites fluid ratios range from 2:1 to 7.5:1. Hydroxyurea concentrates in leukocytes and erythrocytes.

Metabolism

Up to 50% of an oral dose undergoes conversion through metabolic pathways that are not fully characterized. In one minor pathway, hydroxyurea may be degraded by urease found in intestinal bacteria. Acetohydroxamic acid was found in the serum of three leukemic patients receiving hydroxyurea and may be formed from hydroxylamine resulting from action of urease on hydroxyurea.

Excretion

Excretion of hydroxyurea in humans is a nonlinear process occurring through two pathways. One is saturable, probably hepatic metabolism; the other is first-order renal excretion.

Special Populations

Geriatric, Gender, Race

No information is available regarding pharmacokinetic differences due to age, gender or race.

Pediatric

No pharmacokinetic data are available in pediatric patients treated with hydroxyurea.

Renal Insufficiency

There are no data that support specific guidance for dosage adjustment in patients with renal impairment. As renal excretion is a pathway of elimination, consideration should be given to decreasing the dosage of hydroxyurea in patients with renal impairment. Close monitoring of hematologic parameters is advised in these patients.

Hepatic Insufficiency

There are no data that support specific guidance for dosage adjustment in patients with hepatic impairment. Close monitoring of hematologic parameters is advised in these patients.

Drug Interactions

There are no data on concomitant use of hydroxyurea with other drugs in humans.

Animal Pharmacology and Toxicology

The oral LD₅₀ of hydroxyurea is 7330 mg/kg in mice and 5780 mg/kg in rats, given as a single dose.

In subacute and chronic toxicity studies in the rat, the most consistent pathological findings were an apparent dose-related mild to moderate bone marrow hypoplasia as well as pulmonary congestion and mottling of the lungs. At the highest dosage levels (1260 mg/kg/day for 37 days then 2520 mg/kg/day for 40 days), testicular atrophy with absence of

spermatogenesis occurred; in several animals, hepatic cell damage with fatty metamorphosis was noted. In the dog, mild to marked bone marrow depression was a consistent finding except at the lower dosage levels. Additionally, at the higher dose levels (140 to 420 mg or 140 to 1260 mg/kg/week given 3 or 7 days weekly for 12 weeks), growth retardation, slightly increased blood glucose values, and hemosiderosis of the liver or spleen were found; reversible spermatogenic arrest was noted. In the monkey, bone marrow depression, lymphoid atrophy of the spleen, and degenerative changes in the epithelium of the small and large intestines were found. At the higher, often lethal, doses (400 to 800 mg/kg/day for 7 to 15 days), hemorrhage and congestion were found in the lungs, brain, and urinary tract. Cardiovascular effects (changes in heart rate, blood pressure, orthostatic hypotension, EKG changes) and hematological changes (slight hemolysis, slight methemoglo-binemia) were observed in some species of laboratory animals at doses exceeding clinical levels.

INDICATIONS AND USAGE

Significant tumor response to HYDREA (hydroxyurea capsules, USP) has been demonstrated in melanoma, resistant chronic myelocytic leukemia, and recurrent, metastatic, or inoperable carcinoma of the ovary.

Hydroxyurea used concomitantly with irradiation therapy is intended for use in the local control of primary squamous cell (epidermoid) carcinomas of the head and neck, excluding the lip.

CONTRAINDICATIONS

Hydroxyurea is contraindicated in patients with marked bone marrow depression, i.e., leukopenia (<2500 WBC) or thrombocytopenia (<100,000), or severe anemia.

HYDREA is contraindicated in patients who have demonstrated a previous hypersensitivity to hydroxyurea or any other component of its formulation.

WARNINGS

Treatment with hydroxyurea should not be initiated if bone marrow function is markedly depressed (see **CONTRAINDICATIONS**). Bone marrow suppression may occur, and leukopenia is generally its first and most common manifestation. Thrombocytopenia and anemia occur less

often, and are seldom seen without a preceding leukopenia. However, the recovery from myelosuppression is rapid when therapy is interrupted. It should be borne in mind that bone marrow depression is more likely in patients who have previously received radiotherapy of cytotoxic cancer chemotherapeutic agents; hydroxyurea should be used cautiously in such patients.

Patients who have received irradiation therapy in the past may have an exacerbation of postirradiation erythema.

Severe anemia must be corrected with whole blood replacement before initiating therapy with hydroxyurea.

Erythrocytic abnormalities: megaloblastic erythropoiesis, which is self-limiting, is often seen early in the course of hydroxyurea therapy. The morphologic change resembles pernicious anemia, but is not related to vitamin B₁₂ or folic acid deficiency. Hydroxyurea may also delay plasma iron clearance and reduce the rate of iron utilization by erythrocytes, but it does not appear to alter the red blood cell survival time.

Hydroxyurea should be used with caution in patients with marked renal dysfunction.

Elderly patients may be more sensitive to the effects of hydroxyurea, and may require a lower dose regimen.

In patients receiving long-term hydroxyurea for myeloproliferative disorders, such as polycythemia vera and thrombocythemia, secondary leukemia has been reported. It is unknown whether this leukemogenic effect is secondary to hydroxyurea or is associated with the patients' underlying disease.

Carcinogenesis and Mutagenesis

Hydroxyurea is genotoxic in a wide range of test systems and is thus presumed to be a human carcinogen. In patients receiving long-term hydroxyurea for myeloproliferative disorders, such as polycythemia vera and thrombocythemia, secondary leukemia has been reported. It is unknown whether this leukemogenic effect is secondary to hydroxyurea or is associated with the patients' underlying disease. Skin cancer has also been reported in patients receiving long-term hydroxyurea.

Conventional long-term studies to evaluate the carcinogenic potential of hydroxyurea have not been performed. However, intraperitoneal administration of 125-250 mg/kg hydroxyurea (about 0.6-1.2 times the

maximum recommended human oral daily dose on a mg/m^2 basis) thrice weekly for 6 months to female rats increased the incidence of mammary tumors in rats surviving to 18 months compared to control. Hydroxyurea is mutagenic *in vitro* to bacteria, fungi, protozoa, and mammalian cells. Hydroxyurea is clastogenic *in vitro* (hamster cells, human lymphoblasts) and *in vivo* (SCE assay in rodents, mouse micronucleus assay). Hydroxyurea causes the transformation of rodent embryo cells to a tumorigenic phenotype.

Pregnancy

Drugs which affect DNA synthesis, such as hydroxyurea, may be potential mutagenic agents. The physician should carefully consider this possibility before administering this drug to male or female patients who may contemplate conception.

HYDREA (hydroxyurea capsules USP) can cause fetal harm when administered to a pregnant woman. Hydroxyurea is embryotoxic and causes fetal malformations (partially ossified cranial bones, absence of eye sockets, hydrocephaly, bipartite sternbrae, missing lumbar vertebrae) at 180 $\text{mg}/\text{kg}/\text{day}$ (about 0.8 times the maximum recommended human daily dose on a mg/m^2 basis) in rats and at 30 $\text{mg}/\text{kg}/\text{day}$ (about 0.3 times the maximum recommended human daily dose on a mg/m^2 basis) in rabbits. Embryotoxicity was characterized by decreased fetal viability, reduced live litter sizes, and developmental delays. Hydroxyurea crosses the placenta. Single doses of 375 mg/kg (about 1.7 times the maximum recommended human daily dose on a mg/m^2 basis) to rats caused growth retardation and impaired learning ability. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential harm to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

PRECAUTIONS

Therapy with hydroxyurea requires close supervision. The complete status of the blood, including bone marrow examination, if indicated, as well as

kidney function and liver function should be determined prior to, and repeatedly during, treatment. The determination of the hemoglobin level, total leukocyte counts, and platelet counts should be performed at least once a week throughout the course of hydroxyurea therapy. If the white blood cell count decreases to less than $2500/\text{mm}^3$, or the platelet count to less than $100,000/\text{mm}^3$, therapy should be interrupted until the values rise significantly toward normal levels. Severe anemia, if it occurs, should be managed without interrupting hydroxyurea therapy.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

See **WARNINGS** for Carcinogenesis and Mutagenesis information.

Impairment of Fertility: Hydroxyurea administered to male rats at 60 mg/kg/day (about 0.3 times the maximum recommended human daily dose on a mg/m^2 basis) produced testicular atrophy, decreased spermatogenesis, and significantly reduced their ability to impregnate females.

Pregnancy

Pregnancy Category D. (See **WARNINGS**)

Nursing Mothers

Hydroxyurea is excreted in human milk.

Because of the potential for serious adverse reactions with hydroxyurea, a decision should be made either to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Drug Interactions

Prospective studies on the potential for hydroxyurea to interact with other drugs have not been performed.

Concurrent use of hydroxyurea and other myelosuppressive agents or radiation therapy may increase the likelihood of bone marrow depression or other adverse events. (See **WARNINGS** and **ADVERSE REACTIONS**).

Since hydroxyurea may raise the serum uric acid level, dosage adjustment of uricosuric medication may be necessary.

Information for Patients

HYDREA is a medication that must be handled with care. People who are not taking HYDREA should not be exposed to it. If the powder from the capsule is spilled, it should be wiped up immediately with a damp disposable towel and discarded in a closed container, such as a plastic bag.

ADVERSE REACTIONS

Adverse reactions have been primarily bone marrow depression (leukopenia, anemia, and occasionally thrombocytopenia), and less frequently gastrointestinal symptoms (stomatitis, anorexia, nausea, vomiting, diarrhea, and constipation), and dermatological reactions such as maculopapular rash, skin ulceration, dermatomyositis - like skin changes, peripheral and facial erythema. Hyperpigmentation, atrophy of skin and nails, scaling and violet papules have been observed in some patients after several years of long-term daily maintenance therapy with HYDREA. Skin cancer has been reported. Dysuria and alopecia occur very rarely. Large doses may produce moderate drowsiness. Neurological disturbances have occurred extremely rarely and were limited to headache, dizziness, disorientation, hallucinations, and convulsions. HYDREA (hydroxyurea capsules, USP) occasionally may cause temporary impairment of renal tubular function accompanied by elevations in serum uric acid, BUN, and creatinine levels. Abnormal BSP retention has been reported. Fever, chills, malaise, edema, asthenia, and elevation of hepatic enzymes have also been reported.

Adverse reactions observed with combined hydroxyurea and irradiation therapy are similar to those reported with the use of hydroxyurea or radiation treatment alone. These effects primarily include bone marrow depression (anemia and leukopenia), gastric irritation, and mucositis. Almost all patients receiving an adequate course of combined hydroxyurea and irradiation therapy will demonstrate concurrent leukopenia. Platelet depression ($<100,000$ cells/mm³) has occurred rarely and only in the presence of marked leukopenia. HYDREA may potentiate

some adverse reaction usually seen with irradiation alone, such as gastric distress and mucositis.

The association of hydroxyurea with the development of acute pulmonary reactions consisting of diffuse pulmonary infiltrates, fever and dyspnea has been rarely reported. Pulmonary fibrosis also has been reported rarely.

OVERDOSAGE

Acute mucocutaneous toxicity has been reported in patients receiving hydroxyurea at dosages several times the therapeutic dose. Soreness, violet erythema, edema on palms and soles followed by scaling of hands and feet, severe generalized hyperpigmentation of the skin, and stomatitis have been observed.

DOSAGE AND ADMINISTRATION

Procedures for proper handling and disposal of antineoplastic drugs should be considered. Several guidelines on this subject have been published.¹⁻⁷ There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

Because of the rarity of melanoma, resistant chronic myelocytic leukemia, carcinoma of the ovary, and carcinomas of the head and neck in children, dosage regimens have not been established.

All dosage should be based on the patient's actual or ideal weight, whichever is less. Concurrent use of HYDREA with other myelosuppressive agents may require adjustment of dosages.

SOLID TUMORS

Intermittent Therapy

80 mg/kg administered orally as a *single* dose every *third* day.

Continuous Therapy

20 to 30 mg/kg administered orally as a *single dose daily* .

Concomitant Therapy with Irradiation

Carcinoma of the head and neck C 80 mg/kg administered orally as a *single* dose every *third* day.

Administration of hydroxyurea should be begin at least seven days before initiation of irradiation and continued during radiotherapy as well as indefinitely afterwards provided that the patient may be kept under adequate observation and evidences no unusual or severe reactions.

RESISTANT CHRONIC MYELOCYTIC LEUKEMIA

Until the intermittent therapy regimen has been evaluated, CONTINUOUS therapy (20 to 30 mg/kg administered orally as a *single dose daily*) is recommended.

An adequate trial period for determining the antineoplastic effectiveness of hydroxyurea is six weeks of therapy. When there is regression in tumor size or arrest in tumor growth, therapy should be continued indefinitely. Therapy should be interrupted if the white blood cell count drops below $2500/\text{mm}^3$ or the platelet count below $100,000/\text{mm}^3$. In these cases, the counts should be rechecked after three days, and therapy resumed when the counts rise significantly toward normal values. Since the hematopoietic rebound is prompt, it is usually necessary to omit only a few doses. If prompt rebound has not occurred during combined HYDREA (hydroxyurea capsules, USP) and irradiation therapy, irradiation may also be interrupted. However, the need for postponement of irradiation has been rare; radiotherapy has usually been continued using the recommended dosage and technique. Severe anemia, if it occurs, should be corrected without interrupting hydroxyurea therapy. Because hematopoiesis may be compromised by extensive irradiation or by other antineoplastic agents, it is recommended that hydroxyurea be administered cautiously to patients who have recently received extensive radiation therapy or chemotherapy with other cytotoxic drugs.

Pain or discomfort from inflammation of the mucous membranes at the irradiated site (mucositis) is usually controlled by measures such as topical anesthetics and orally administered analgesics. If the reaction is severe, hydroxyurea therapy may be temporarily interrupted; if it is extremely severe, irradiation dosage may, in addition, be temporarily postponed. However, it has rarely been necessary to terminate these therapies.

Severe gastric distress, such as nausea, vomiting, and anorexia, resulting from combined therapy may usually be controlled by temporary interruption of hydroxyurea administration.

Renal Insufficiency

There are no data that support specific guidance for dosage adjustment in patients with renal impairment. As renal excretion is a pathway of elimination, consideration should be given to decreasing the dosage of HYDREA in patients with renal impairment. Close monitoring of hematologic parameters is advised in these patients.

Hepatic Insufficiency

There are no data that support specific guidelines for dosage adjustment in patients with hepatic impairment. Close monitoring of hematologic parameters is advised in these patients.

HOW SUPPLIED

HYDREA® (hydroxyurea capsules, USP)

500 mg capsules in bottles of 100 (NDC 0003-0830-50).

Capsule identification number: 830.

Storage

Store at room temperature; avoid excessive heat. Keep tightly closed.

REFERENCES:

1. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. NIH Publication No. 83-2621. For sale by the Superintendent of Documents, US Government Printing Office, Washington, DC 20402.
2. AMA Council Report. Guidelines for Handling Parenteral Antineoplastics. JAMA 1985; 253(11):1590-1592.
3. National Study Commission on Cytotoxic Exposure -- Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, ScD, Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, MA 02115.
4. Clinical Oncological Society of Australia. Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. Med J Australia 1983; 1:426-428.

5. Jones RB, et al. Safe Handling of Chemotherapeutic Agents: A Report from the Mount Sinai Medical Center, CA-A Cancer Journal for Clinicians 1983; (Sept/Oct) 258-263.
6. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. Am J Hosp Pharm 1990; 47:1033-1049.
7. OSHA Work-Practice Guidelines for Personnel Dealing with Cytotoxic (Antineoplastic) Drugs. Am J Hosp Pharm 1986; 43:1193-1204.



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